

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
27 January 2005 (27.01.2005)

PCT

(10) International Publication Number
WO 2005/007193 A2

(51) International Patent Classification⁷: **A61K 45/06**

(21) International Application Number:
PCT/US2004/021641

(22) International Filing Date: 7 July 2004 (07.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/484,676 7 July 2003 (07.07.2003) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

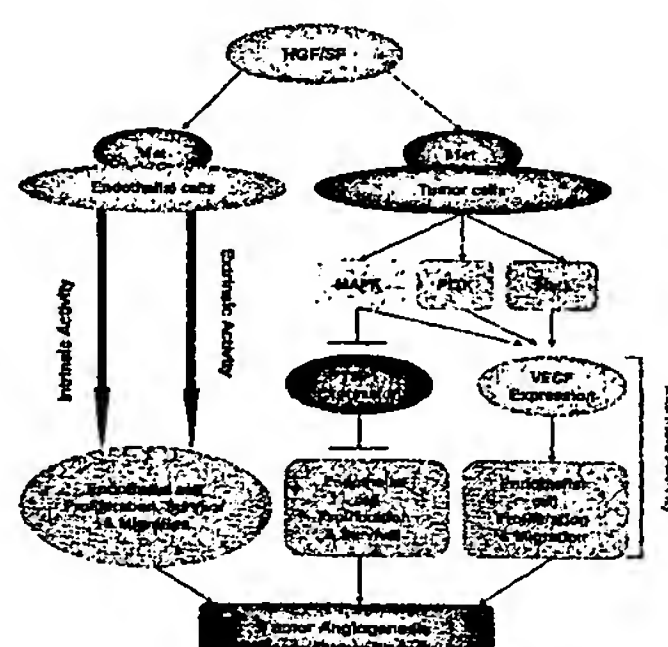
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: INHIBITION OF TUMOR ANGIOGENESIS BY COMBINATION OF THROMBOSPONDIN-1 AND INHIBITORS
OF VASCULAR ENDOTHELIAL GROWTH FACTOR



(57) Abstract: Hepatocyte growth factor/scatter factor (HGF/SF), acting through the Met receptor, plays an important role in most human solid tumors and inappropriate expression of this ligand-receptor pair is often associated with poor prognosis. The molecular basis for the malignant activity imparted by signaling of HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF also induces angiogenesis, but the signaling mechanism has not been understood, nor has this activity been directly associated with HGF/SF-Met mediated tumorigenesis. HGF/SF induces expression *in vitro* of VEGF, a key agonist of tumor angiogenesis. By contrast, thrombospondin-1 (TSP-1) is a negative regulator of angiogenesis. This application discloses that, in the very same tumor cells, in addition to inducing VEGF expression, HGF/SF dramatically down regulates TSP-1 expression. TSP shut off plays an important, extrinsic role in HGF/SF-mediated tumor development, as ectopic expression of TSP-1 markedly inhibited tumor formation through the suppression of angiogenesis. While VEGF induced expression is sensitive to inhibitors of several pathways, including MAP kinase, P13 kinase and Stat3, TSP-1 shut off by HGF/SF is prevented solely by inhibiting MAP kinase activation. Thus HGF/SF is a "switch" for turning on angiogenesis. TSP-1 is a useful antagonist to tumor angiogenesis, and therefore TSP-1 and agonist peptides and mimics, as well as inducers of TSP-1, have therapeutic value when used in conjunction with inhibitors of VEGF.



WO 2005/007193 A2